Consensus Guidelines

Dermatology

Dermatology 2016;232:385–406
DOI: 10.1159/000445681

Received: March 20, 2016
Accepted: March 20, 2016
Published online: June 21, 2016

Swiss S1 Guidelines on the Systemic Treatment of Psoriasis Vulgaris

Antonios G.A. Kolios[a, b] Nikhil Yawalkar[c] Mark Anliker[d] Wolf-Henning Boehncke[e] Luca Borradori[c] Curdin Conrad[f] Michel Gilliet[f] Peter Häusermann[g] Peter Itin[g] Emmanuel Laffitte[e] Carlo Mainetti[h] Lars E. French[a] Alexander A. Navarini[a]

Departments of [a]Dermatology and [b]Immunology, Zurich University Hospital, Zurich, [c]Department of Dermatology, Bern University Hospital, Bern, [d]Department of Dermatology and Allergies, St. Gallen Cantonal Hospital, St. Gallen, [e]Division of Dermatology and Venereology, Geneva University Hospital, Geneva, [f]Department of Dermatology and Venereology, Lausanne University Hospital, Lausanne, [g]Department of Dermatology, Basel University Hospital, Basel, and [h]Department of Dermatology, Regional Hospital of Bellinzona, Bellinzona, Switzerland

Key Words
Swiss guidelines on psoriasis vulgaris · Systemic treatment of psoriasis · Systemic treatment recommendations · Transitioning of systemic therapies · Biologicals · Small molecules · Psoriasis

Abstract
Psoriasis vulgaris is a common, chronic inflammatory skin disease with a prevalence of 1.5–2% in Western industrialized countries. A relevant percentage of patients suffer from moderate-to-severe psoriasis and experience a significant reduction in quality of life. The choice of an adequate therapy could help to prevent disease and exacerbation of comorbidity, which could increase quality of life, avoid hospitalization and avoid reduction of working days. The present guidelines are focused on the initiation and management of systemic therapies in cases of moderate-to-severe plaque-type psoriasis in adults to optimize treatment response, adherence and quality of life. This first version of the Swiss S1 guidelines presents therapeutic recommendations which are based on a systematic literature search as well as an informal expert consensus of dermatologists in Switzerland.

Introduction

On behalf of the Swiss Society of Dermatology and Venereology SGDV/SSDV, the Swiss Dermatology Network for Targeted Therapies has prepared an evidence-based guideline for the treatment of plaque-type psoriasis. This work is partially based on previously published Swiss recommendations [1, 2], the updated German S3 guidelines [3] and the European S3 guideline for psoriasis [4]. The goal of the Swiss S1 guidelines is to develop an informal expert consensus to provide a strategy management of systemic therapies by Swiss dermatologists and to focus on induction therapy in cases of moderate-to-severe plaque-type psoriasis in adults, as well as to include useful Swiss-specific aspects and regulatory issues. The varieties of a patient's disease aspects with their medical history, therapy preferences, comorbidities including psoriatic arthritis, childbearing potential, risk of infection, adherence, long-term safety and much more are major points in the decision between patients and their treating physicians to choose the right medication to treat psoriasis and have to be evaluated in the individual patient's consultation.

In Western industrialized nations, psoriasis has a prevalence of 1.5–2%. About 80% of those afflicted suffer from the plaque form, and more than 90% are chronic [5].

KARGER

E-Mail karger@karger.com
www.karger.com/drm

1018–8665/16/2324–0385$39.50/0

Alexander A. Navarini
Department of Dermatology, Zurich University Hospital
Gloriastrasse 31
CH–8091 Zurich (Switzerland)
E-Mail alexander.navarini@usz.ch

Depending on the severity of disease and related disability as well as psychosocial stigmatization, the quality of life can be considerably impaired [6], comparable to patients with type 2 diabetes, cancer and chronic lung disease [7]. Nevertheless, in the past, adherence to therapies was observed to be relatively low. Before the advent of biological therapies, only 25% of patients were very satisfied with the results of their therapy for psoriasis [8], resulting in a high rate of nonadherence of up to 40% [9, 10]. In addition, patients reported lack of information about potential side effects of drugs, complicated usage, poor tolerability, fear, costs, and low efficacy [11, 12]. Dermatologists have high expertise in managing topical drugs, but 76% are somewhat uncertain about prescribing systemic medications [13]. Thus, about 50% of moderate-to-severe psoriasis patients are treated with topicals alone [14]. However, the choice of an adequate therapy could help to prevent disease and exacerbation of comorbidity which could increase quality of life, avoid hospitalization and avoid reduction of working days, which is also recognized by the World Health Organization [15, 16].

Systemic Treatment Options in Moderate-to-Severe Chronic Plaque Psoriasis

Moderate-to-severe psoriasis is defined as Psoriasis Area and Severity Index (PASI) >10 or body surface area (BSA) >10% and/or Dermatology Life Quality Index (DLQI) >10 [17]. The Swiss guideline expert panel unanimously supports this definition and urges insurances and policy makers to accept DLQI >10 as official threshold.

This becomes important in severe involvement of special locations, particularly in areas such as the scalp, genitals, palms and/or soles, nail involvement, presence of single recalcitrant plaques or pruritus leading to scratching. Severe involvement of visible areas but not high BSA is not reflected by representative values of the PASI. Localized tools like palmoplantar PASI (online suppl. calculator; see www.karger.com/doi/10.1159/000445681 for all online suppl. material) [18] and Nail Psoriasis Severity Index [19] have been suggested but are not generally used for severity assessment in special localizations. Especially nail, palmoplantar and inguinal involvement has a severe impact on quality of life. Here the DLQI should be considered for the evaluation of the psoriasis severity.

The PASI is a standard tool to define disease severity in psoriasis as well as the BSA, DLQI, Physician's Global Assessment or Investigator's Global Assessment [20–23]. An adapted PASI calculation, the Precise PASI, utilizes the same source data as the PASI but does not neglect the percentages of surface involvement, achieving a much higher resolution in the lower BSA ranges (<5%) [24].

The current systemic treatment options in Switzerland for moderate-to-severe psoriasis include small molecules and biologicals. The former group encompasses small molecules such as methotrexate (MTX), cyclosporine A (CsA), apremilast (APR), fumaric acid esters (FAEs) and acitretin. The latter group includes the tumor necrosis factor (TNF)-α antagonists adalimumab (ADA), etanercept (ETA), and infliximab (IFX), the p40 interleukin (IL)-12/23 antagonist ustekinumab (UST) and the IL-17A antagonist secukinumab (SEC). FAEs are not formally registered for the treatment of psoriasis in Switzerland.

Before any of the above treatments are prescribed, external skin care and topical drugs should be used to the fullest extent, namely emollients, topical drugs such as corticosteroids, vitamin D derivates and tacrolimus/pimecrolimus, as well as phototherapy such as narrowband UVB, UVA or topical/systemic PUVA. These are often additionally used in moderate-to-severe psoriasis as a first-line treatment. Only when insufficient efficacy of these treatments is confirmed, systemic agents should be used. In Switzerland biologicals can be used exclusively in patients who were unsuccessfully treated with at least one conventional systemic therapy and/or phototherapy (limitation for biologicals by insurance/governmental regulations). In addition, IFX is reimbursed only after failure of a previous TNF-α inhibitor and a treatment duration of 1 year but can be extended by permission of the insurance in case of positive treatment success.

Acitretin

Acitretin is a retinoid (vitamin A derivate) that can be used for moderate-to-severe psoriasis vulgaris, as well as local or generalized pustular or erythrodermic psoriasis. In contrast to other systemic therapies, it is not considered cytotoxic or immunosuppressive. This is considered an advantage for patients with malignant tumors. Also, it has an antiproliferative effect that is partially preventive for epithelial tumors of the skin [5, 25, 26].

Induction therapy for plaque psoriasis is started with 10–20 mg/day (0.3–0.5 mg/day/kg body weight) for 4 weeks, and then slowly increased until patients notice a slight scaliness on the lips which is an indicator for sufficient bioavailability. The general maintenance dose is recommended between 25 and 50 mg/day (0.5–0.8 mg/kg

body weight) depending on efficacy and tolerability. Doses up to 20 mg daily do not usually lead to a satisfactory response but have no or only mild side effects [26]. Capsules should be ingested with whole milk or a fatty meal. Combination therapies have been described with UV phototherapy (narrow-band UVB, broad-band UVB, UVA and PUVA) as well as MTX, cyclosporine, TNF inhibitors and UST [27].

Because of the high teratogenicity, double contraception is mandatory for women during and up to 2 years after discontinuation (e.g. condom + pill; intrauterine device/Nuva-Ring + pill; please note: *no* low-dosed progesterone preparations/minipills). Monthly pregnancy tests are recommended in women of childbearing age; see table 2 for the prevention of adverse events [5]. The patient should be asked about spine/joint complaints at follow-up visits; if yes without a hint for psoriatic arthritis (PsA), further imaging should be performed due to the possibility of diffuse idiopathic skeletal hyperostosis which occurs in less than 1% of patients. Depression is not listed as an official side effect in patients treated with acitretin but is described very rarely.

Headache, nausea and/or vomiting, fatigue, irritability, and pruritus are symptoms of acute overdose. In this case, discontinue retinoids, monitor vital parameters/liver and renal function/electrolytes and consult specialists to manage extracutaneous side effects (tables 1, 2).

Absolute Contraindications

- Severe renal or hepatic dysfunction
- Hepatitis
- Women of childbearing age: pregnancy, breast-feeding, desire to have children or insufficient guarantee of effective contraceptive measures up to 2 years after discontinuation of therapy
- Excessive alcohol consumption
- Incompatible comedication
- Unwillingness to cease blood donation during and until 1 year after treatment
- Hypersensitivity to acitretin

Relative Contraindications

- Alcohol abuse
- Diabetes mellitus
- Contact lenses
- Childhood
- History of pancreatitis
- Hyperlipidemia (particularly hypertriglyceridemia) and drug-controlled hyperlipidemia
- Atherosclerosis

Table 1. Overview of important side effects of acitretin [27, 30]

Frequency	Side effects
Very frequent	Vitamin A toxicity (xerosis, cheilitis)
Frequent	Conjunctival inflammation (check contact lenses), hair loss, photosensitivity, hyperlipidemia
Occasional	Muscle, joint, and bone pain, retinoid dermatitis
Rare	Gastrointestinal complaints, hepatitis, jaundice, bone changes with long-term therapy
Very rare	Idiopathic intracranial hypertension, decreased color vision and impaired night vision

Table 2. Prevention of side effects of acitretin

Prevention of adverse events	Action
Dry skin or mucous membranes	Apply ointment (also to nasal mucosa if needed), eyedrops, avoid wearing contact lenses
Diffuse alopecia	Inform patient of reversible nature of the side effect, consider stopping treament
Light sensitivity	Avoid exposure to sunlight, use sunscreen
Increased serum lipids and/or liver values	Alcohol abstinence, low-fat/low-carbohydrate diet, lipid-lowering drug (gemfibrozil or atorvastatin); if levels fluctuate: monitor frequency and discontinue therapy if necessary
Muscle and bone pain	If symptoms persist: X-rays, NSAIDs, avoid excessive physical activity, consider PsA
Generalized edema (rare)	Stop treatment, check kidney function

Limitation (FOPH)

Severe, therapy-refractory cases of psoriasis [as limitation, reimbursement criteria of the Federal Office of Public Health (FOPH, in German Bundesamt für Gesundheit, BAG) are considered].

Apremilast

Apremilast (APR, Otezla®) is a small molecule inhibiting intracellular phosphodiesterase-4. It is indicated in patients with moderate-to-severe plaque psoriasis who failed light therapy, MTX, cyclosporine, acitretin or PUVA and is also indicated in psoriatic arthritis patients

Table 3. Overview of important side effects of apremilast [28]

Frequency	Side effect
Very frequent	Diarrhea, nausea
Frequent	Bronchitis, upper respiratory tract infections, nasopharyngitis, decreased appetite, insomnia, migraine, (tension) headache, cough, vomiting, dyspepsia, frequent bowel movements, upper abdominal pain, gastroesophageal reflux disease, back pain, fatigue
Occasional	Hypersensitivity, rash, weight decrease
Rare	None
Very rare	None
Frequency not reported (causal connection unclear)	Depression, urinary tract infection, coronary artery disease, acute myocardial infarction, chronic obstructive pulmonary disease, nephrolithiasis, osteoarthritis, psoriatic arthropathy, diverticulitis, pneumonia, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, breast cancer, renal cell carcinoma, vasculitis

Table 4. Dosing scheme (mg) for initiation of apremilast therapy

Day	Morning	Evening
Day 1	10	–
Day 2	10	10
Day 3	10	20
Day 4	20	20
Day 5	20	30
Day 6 and ongoing	30	30

who failed disease-modifying antirheumatic drugs (table 3).

The recommended dosage is 30 mg p.o. twice daily for maintenance; see table 4 for induction scheme.

In case of infection during treatment, stop temporarily.

Absolute Contraindications

- Rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption
- Pregnancy/breast-feeding
- Hypersensitivity to apremilast
- Live vaccines

Relative Contraindications

- In patients with severe renal impairment (creatinine clearance of less than 30 ml/min estimated by the Cockcroft-Gault equation), the dose should be reduced to 30 mg once daily
- Caution in case of depression
- Underweight at the start of treatment should be monitored regularly; in case of unexplained and clinically significant weight loss, evaluate the patient and consider discontinuation of APR.

With lack of data or recommendations, the following medical states should be considered very carefully: active and latent tuberculosis, acute or severe infections, history of or active chronic hepatitis B and C, HIV, live vaccines, malignancies (apart from successfully treated nonmelanoma skin cancer and cervical dysplasia) and lymphoproliferative disorders. Diarrhea is rather transient over the first weeks of treatment.

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis who did not experience therapeutic success with UVB and PUVA or one of the following systemic therapies: cyclosporine, MTX, acitretin. The treatment has to be stopped in case of no therapeutic success after 24 weeks. Not in combination with biologicals. For psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics.

Cyclosporine A

CsA is indicated for moderate-to-severe psoriasis (as well as rescue therapy for erythrodermic and pustular psoriasis), especially in induction therapy [29]. A combination with topical steroids and vitamin D analogs may be recommended and reduce the dosage of CsA. Due to side effects such as nephrotoxicity, increased cancer risk and arterial hypertension, therapy is limited to 1 year [5].

CsA capsules contain 12.7% of alcohol which has to be taken into account in patients with liver diseases, alcohol abuse, epilepsy, brain injuries, pregnancy, breast-feeding women and children. CsA itself shows no teratogenicity but may be associated with preeclampsia, premature birth and low birth weight.

There are a lot of possible interactions with other drugs, especially statins, with an increased risk of myopathies. Side effects are possibly dose dependent and disappear with dose reduction (table 5).

Table 5. Overview of important side effects of CsA [4, 30]

Frequency	Side effects
Very frequent	None
Frequent	Renal failure (dose-dependent), danger of irreversible renal damage (long-term therapy), hypertension, gingival hyperplasia, reversible hepatogastric complaints (dose-dependent), tremor, weariness, headache, burning sensation in hands and feet, reversibly elevated blood lipids (especially in combination with corticosteroids), hypertrichosis
Occasional	Seizures, gastrointestinal ulcerations, weight gain, hyperglycemia, hyperuricemia, hyperpotassemia, hypomagnesemia, acne, anemia
Rare	Ischemic heart disease, pancreatitis, motor polyneuropathy, impaired vision, defective hearing, central ataxia, myopathy, erythema, itching, leukopenia, thrombocytopenia
Very rare	Microangiopathic hemolytic anemia, hemolytic uremic syndrome, colitis (isolated cases), papillary edema (isolated cases), idiopathic intracranial hypertension (isolated cases)

The combination of CsA and excessive phototherapy leads to an increased risk of squamous cell carcinoma [5].

Handling of Side Effects [25]

- If serum creatinine is increased (5–30%, in up to 20% increase in creatinine by more than 30%):
  - ≤30% of baseline value should prompt a revision of the patient's fluid intake
  - 30–50% of baseline value (even if in the normal range), a dose reduction of 25% is recommended
  - ≥50% of baseline value should lead to a dose reduction of 50%
  - If after 30 days an increase of ≥30% persists, stop CsA; calculate creatinine clearance (reduced in up to 20% of patients)
- Arterial hypertension (2–5%) requires an antihypertensive therapy if blood pressure is ≥160/90 mm Hg in two consecutive measurements. However, calcium antagonists could raise CsA levels, and angiotensin-converting enzyme inhibitors/angiotensin-2 receptor antagonists could induce hyperpotassemia. If despite an antihypertensive therapy the blood pressure is still increased, a CsA dose reduction of 25% is necessary, with subsequent stop in case of insufficient response
- Hypomagnesemia (about 5–15%): substitute 200 mg/day, possibly more
- Hyperpotassemia (>5.0 mmol/l): potassium-deficient nutrition, ensure sufficient fluid intake (2–3 l/day), reduce CsA by 25%, acute management of severe hyperpotassemia (≥6.0 mmol/l)
- Elevation of bilirubin (10–80%) or transaminases (up to 30%) by twice the upper limit of normal should lead to a dose reduction by 25% and laboratory control after 30 days; if still elevated, consider CsA cessation
- Elevation of blood lipids (fasting cholesterol and triglycerides) should be answered with a low-cholesterol- and low-fat diet, dose reduction, or stop of CsA, respectively. Statins or fibrates are not recommended due to the risk of restriction of renal function and myalgia to rhabdomyolysis
- Gingival hyperplasia (in up to 15%): optimal dental hygiene, dose reduction, if persistent, stop CsA. More frequent in case of concomitant nifedipine treatment

Interactions

There are several interactions that need to be checked before initiation of treatment. CsA can reduce the efficacy of progesterone-containing contraceptives. Sufficient contraception has to be ensured.

- Increase in the cyclosporine level (CYP3A inhibition) due to: grapefruit juice, allopurinol, calcium antagonists, amiodarone, antibiotics (macrolides, clarithromycin, josamycin, ponsinomycin, pristinamycin, doxycycline, gentamicin, tobramycin, ticarcillin, quinolones), ketoconazole, oral contraceptives, methylprednisolone (high dosages), ranitidine, cimetidine
- Decrease in the cyclosporine level (CYP3A induction) due to: carbamazepine, phenytoin, barbiturates, metamizole, St. John's wort
- Possible reinforcement of nephrotoxic adverse drug reactions by: aminoglycosides, amphotericin B, ciprofloxacin, acyclovir, nonsteroidal antiphlogistics
- Specific interactions:
  - Potassium-saving substances: increased risk of hyperpotassemia
  - Reduced clearance of: digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (e.g. lovastatin), diclofenac

Absolute Contraindications [25]

- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease

- History of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma in situ)
- Current malignancy
- Simultaneous PUVA therapy

Relative Contraindications [25]
- Previous potential carcinogenic therapies (e.g. arsenic, PUVA >1,000 J/cm^2)
- Psoriasis triggered by severe infection or drugs (β-blockers, lithium, antimalarial drugs)
- Significant hepatic diseases
- Hyperuricemia
- Hyperkaliemia
- Simultaneous therapy with nephrotoxic drugs (see drug interactions)
- Simultaneous phototherapy (selective UV therapy, except PUVA, see above)
- Simultaneous use of other systemic immunosuppressive agents
- Simultaneous use of systemic retinoids or therapy with retinoids in the last 4 weeks prior to planned onset of therapy with cyclosporine
- Drug or alcohol-related diseases
- Long-term previous treatment with MTX
- Pregnancy/breast-feeding
- Vaccination with live vaccines
- Epilepsy
- Current treatment with castor oil preparations

In case of CsA overdosing, CsA should be stopped, drug levels for CsA should be measured; vital parameters, liver and kidney function as well as electrolytes should be measured.

Limitation (FOPH)

None for psoriasis. It is however common practice to prescribe CsA for psoriasis without prior confirmation of coverage.

Fumaric Acid Esters

FAEs in psoriasis have been known since 1959, but FAEs have so far been registered only in Germany in 1995. Due to tolerability (table 6), FAEs are slowly introduced via Fumaderm initial® (contains 30 mg dimethylfumarate) and Fumaderm® (contains 120 mg dimethylfumarate); see table 7 for a recommended dosage scheme.

Table 6. Overview of important side effects of FAEs [4]

Frequency	Side effects
Very frequent	Diarrhea, flush, mild leukopenia and lymphopenia (approx. 50% of patients)
Frequent	Abdominal cramps, flatulence, severe lymphocytopenia (approx. 3% of patients), transient eosinophilia
Occasional	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes
Rare	Allergic skin reaction
Very rare	None

Table 7. Dosing scheme (tablets) for FAE therapy

	Fumaderm® initial	Fumaderm®
Week 1	1–0–0	
Week 2	1–0–1	
Week 3	1–1–1	
Week 4		1–0–0
Week 5		1–0–1
Week 6		1–1–1
Week 7		2–1–1
Week 8		2–1–2
Week 9 and ongoing		2–2–2

Up to 60% of patients suffer from transient gastrointestinal side effects in the first few weeks. In severe cases it is necessary to reduce the dosage and to discontinue treatment. The intake of FAEs with milk products can improve its gastrointestinal tolerability, as can a regular and stable time point during the day for drug intake. After increasing the dose up to Fumaderm® 2–2–2 tablets and/or a dose with a satisfactory psoriasis response, the maintenance dosage can be reduced based on individual treatment requirements.

FAEs have relatively few drug interactions (less than 5%) and can be used also in comorbid patients on a case-by-case basis [30–32]. Prior to prescription, the reimbursement must be confirmed for every single patient by the respective health insurance [3].

Contraindications [33]
- Severe general disease
- Chronic gastrointestinal diseases

- Severe liver and kidney diseases
- Chronic diseases accompanied by disturbances in leukocyte counts and functions
- Malignancies
- Pregnant or lactating women
- Hypersensitivity to FAEs

Limitation (FOPH)

FAEs are off label in Switzerland and need to be imported by an international pharmacy. It is obligatory to seek reimbursement of the health insurance provider prior to prescribing FAEs.

Methotrexate

MTX is indicated for moderate-to-severe psoriasis and can also be efficacious in pustular or erythrodermic forms. MTX is also indicated in psoriatic arthritis. There is still no clear consensus about the use of folic acid during MTX treatment. It could be shown that folic acid reduces the incidence of abnormal liver function tests and withdrawal from treatment as well as a trend towards a reduction in gastrointestinal side effects and stomatitis. 5 mg folic acid at least 24 h after MTX is commonly used, or it can also be taken 24 h before MTX in case of persisting gastrointestinal side effects [34, 35] (table 8). Contraception (women and men) is warranted during treatment and should be continued for 3 months after treatment discontinuation. More frequent laboratory tests are required in patients with an increased risk of elevated MTX levels (dehydration, diminished renal function) or when increasing the dosage.

It is recommended to perform a chest X-ray before MTX initiation as a baseline image to compare against in case of signs of pneumonitis (table 9). In up to 8% of the patients an MTX-induced pneumonitis occurs [36]. The determination of procollagen III N-terminal peptide is controversial but recommended in the European and German S3 psoriasis guidelines and others [4, 37–39].

Absolute Contraindications [25]

- Severe infections
- Severe liver disease
- Renal failure
- Conception (men and women)/breast-feeding
- Alcohol abuse
- Bone marrow dysfunction/hematological changes
- Immunodeficiency
- Acute peptic ulcer

Table 8. Overview of important side effects of MTX [4, 30, 34]

Frequency	Side effects
Very frequent	Nausea, malaise, hair loss
Frequent	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers, pneumonitis
Occasional	Fever, chills, depression, infections
Rare	Nephrotoxicity, liver fibrosis and cirrhosis
Very rare	Interstitial pneumonia, alveolitis

Table 9. Symptoms of MTX-induced pneumonitis

1	Acute onset of dyspnea
2	Fever >38° C
3	Tachypnea >28/min and dry cough
4	Radiological findings of interstitial or alveolar infiltrates
5	Leukocytosis ≤15,000 cells/mm^3
6	Negative blood culture and expectorate cultures
7	Restrictive ventilation disorder in pulmonary function test and reduced CO_2 diffusing capacity (<70%)
8	pO_2 <7.5 kPa
9	Histology of bronchiolitis or interstitial pneumonitis with giant cells and lack of signs of infection

Diagnosis of MTX-induced pneumonitis is:
Certain, if >6 of 9 criteria are positive
Probable, if >5 of 9 criteria are positive
Possible, if 4 of 9 criteria are positive

- Significantly reduced lung function
- Hypersensitivity to MTX

Relative Contraindications [25]

- Kidney or liver disorders
- Ulcerative colitis
- History of hepatitis
- Lack of compliance
- Active desire to have a child for women of childbearing age and men
- Gastritis
- Diabetes mellitus
- Previous malignancies
- Congestive heart failure

Acute toxicity includes myelosuppression, mucosal (especially oral) ulceration and rarely cutaneous necrosis (especially if the dosage of MTX is increased too rapidly) [34]. Calcium leucovorin serves as antidote to MTX-induced hematological toxicity, but its efficacy decreases

with the delay after administration of MTX. In case of overdose, calcium leucovorin should be administered at 20 mg (or 10 mg/m^2) i.v. or i.m. and repeated every 6 h intravenously, intramuscularly or orally (if given orally the dose of leucovorin should be increased by 15 mg). MTX levels should be measured every 12–24 h until the serum MTX concentration is below 10^{-8} mol/l. If MTX levels are not available, continue giving leucovorin until the blood count has normalized and mucosal lesions have healed. To increase drug survival by inhibition of the development of antidrug antibodies or enhancing efficacy, concomitant MTX is often added to TNF inhibitor treatment, especially in patients receiving IFX [40, 41].

Limitation (FOPH)

None for psoriasis. It is however common practice to prescribe MTX for psoriasis without prior confirmation of coverage.

Adalimumab

ADA (Humira®) is a recombinant human IgG1 monoclonal antibody binding soluble and membrane-bound TNF-α [42] and is indicated for moderate-to-severe psoriasis patients who failed a prior treatment with at least one conventional systemic drug or phototherapy. ADA is also indicated in psoriatic arthritis. The recommended dosage is 80 mg s.c. on day 0 for induction, followed by 40 mg s.c. every other week beginning 1 week after induction for maintenance of treatment.

In case of infection during treatment, stop temporarily. In case of pregnancy, stop until the end of pregnancy and restart not earlier than 5 months after the last ADA injection, which counts also for breast-feeding. ADA should be discontinued 4–8 weeks prior to and may be restarted 2–3 weeks after a live attenuated vaccination [34]. Patients should be informed about the potential risk for serious and atypical infections and in case of symptoms should seek medical advice. The material of the ADA syringe or pen is to be latex free (table 10).

Table 10. Overview of important side effects of ADA [30]

Frequency	Side effect
Very frequent	Injection site reaction
Frequent	Upper respiratory tract infections, sinusitis, headache, rash
Occasional	Tuberculosis, reactivation of latent tuberculosis, TNF-α-induced lupus-like syndrome, paradoxical psoriasis
Rare	Lymphoma
Very rare	None

Absolute Contraindications [4]

- Concomitant immunosuppressive therapy
- Active chronic hepatitis B
- Active tuberculosis
- Congestive heart failure (NYHA grade III/IV)
- Pregnancy/breast-feeding
- Hypersensitivity to ADA

Relative Contraindications [4]

- History of recurrent infections
- Underlying conditions predisposing to infections
- Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis
- Live attenuated vaccines
- Localized infections
- Latent tuberculosis
- Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
- Hepatitis C
- >200 PUVA treatments (especially if followed by cyclosporine use)
- Malignancies (apart from successfully treated nonmelanoma skin cancer and cervical dysplasia) and lymphoproliferative disorders

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis who did not experience therapeutic success with UVB and PUVA or one of the following systemic therapies: cyclosporine, MTX, acitretin. The treatment has to be stopped in case of no therapeutic success after 12 weeks. For psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics.

Etanercept

ETA (Enbrel®) is a soluble TNF receptor Fc fusion protein which binds soluble and membrane-bound TNF-α as well as lymphotoxin-β [42] and is indicated for moderate-to-severe psoriasis patients who failed a prior treatment with at least one conventional systemic drug or phototherapy. ETA is also indicated in psoriatic ar-

Table 11. Overview of important side effects of ETA [30]

Frequency	Side effect
Very frequent	Injection site reactions, infections (upper respiratory tract, bronchitis, skin)
Frequent	Pruritus, fever, allergic reactions
Occasional	Serious infection, urticaria, angioedema, thrombocytopenia, nonmelanoma skin cancers, uveitis, interstitial lung disease, vasculitis, psoriasis (including new onset or worsening and pustular)
Rare	Opportunistic infections, tuberculosis, Stevens-Johnson syndrome, erythema multiforme, pancytopenia, anemia, leukopenia, neutropenia, serious allergic reactions/anaphylactic reactions, elevated liver enzymes, autoimmune hepatitis, CNS-demyelinating events (e.g. multiple sclerosis), localized demyelinating events (e.g. optic neuritis, transverse myelitis), seizures, worsening of congestive heart failure, cutaneous vasculitis, cutaneous lupus, lupus-like syndrome, lymphoma, melanoma
Very rare	Toxic epidermal necrolysis, demyelinating polyneuropathy including Guillain-Barré syndrome, aplastic anemia

thritis. The recommended initial dosage is 1 × 50 mg or 2 × 50 mg weekly over 12 weeks followed by a maintenance dosage of 1 × 50 mg weekly. 2 × 50 mg for the induction phase has a faster onset compared to 1 × 50 mg [43].

In case of infection during treatment, stop temporarily, and in case of pregnancy, stop until the end of pregnancy and breast-feeding. ETA can be discontinued without any relevant loss of efficacy at re-initiation as no neutralizing antibodies against ETA are produced [44]. ETA should be discontinued 4–8 weeks prior to and may be restarted 2–3 weeks after a live attenuated vaccination. Patients should be informed about the potential risk for serious and atypical infections and in case of symptoms should seek medical advice. The removable cap of the SureClick® autoinjector and the prefilled syringe contain latex which may cause an allergic reaction in latex-sensitive individuals (table 11).

Absolute Contraindications [4]

- Active (chronic) infections (including tuberculosis and active chronic hepatitis B)
- Congestive heart failure (NYHA grade III or IV)
- Hypersensitivity to ETA

Relative Contraindications [4]

- Pregnancy/breast-feeding
- >200 PUVA treatments (especially if followed by cyclosporine use)
- HIV or AIDS
- Hepatitis C and B
- Congestive heart failure (NYHA grade I or II)
- Demyelinating disease (also family history)
- Malignancies (apart from successfully treated nonmelanoma skin cancer and cervical dysplasia) or lymphoproliferative disorders
- Live attenuated vaccines

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis who did not experience therapeutic success with UVB and PUVA or one of the following systemic therapies: cyclosporine, MTX, acitretin. The treatment has to be stopped in case of no therapeutic success after 12 weeks. For psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics. Cost coverage has to be granted by the patient's health insurance.

Infliximab

IFX (Remicade®) is a chimeric (mouse/human) monoclonal antibody binding soluble and membrane bound TNF-α [42] and is indicated for moderate-to-severe psoriasis patients who failed a prior treatment with at least one conventional systemic drug or phototherapy and at least one TNF-α antagonist treatment. IFX is also indicated in psoriatic arthritis. IFX is the only available intravenous biological for psoriasis and is available as powder in 100-mg vials which should be stored at 2–8°C and reconstituted in 10 ml sterile water. The total dosage should be diluted with 250 ml of 0.9% saline solution, infused over a period of 2 h and monitored 1 h after treatment. The recommended dosage is 5 mg/kg body weight at weeks 0, 2 and 6 for induction followed by infusions every 8 weeks.

In rheumatological conditions, IFX is often combined with MTX to improve long-term efficacy. It could additionally be shown that the treatment survival rates of all three TNF-α antagonists are better in combination with MTX [40, 45]. In case of overdose, the patient should be followed closely for adverse events, particularly infections (table 12).

Table 12. Overview of important side effects of IFX [30]

Frequency	Side effect
Very frequent	Infusion reactions, headache, viral infections (influenza, herpes virus infections)
Frequent	Bacterial infections (sepsis, cellulitis), flush, pruritus, urticaria, hypotension, hypertension, fever, transaminase elevation, dizziness
Occasional	Serum-sickness-like disease, (cutaneous) lupus erythematosus syndrome, heart failure, severe infections, tuberculosis, anaphylactoid reaction
Rare	Opportunistic infections, pancytopenia, vasculitis, melanoma, leukemia, lymphoma, non-Hodgkin lymphoma, demyelinating diseases
Very rare	None

Managing of Side Effects

Infusion reactions occur in about 20% of patients with an increased risk in patients who developed antibodies against IFX. Most reactions are mild to moderate (flush, pruritus, chills, headache, urticaria), and about 1% are severe (anaphylactic reactions, serum-sickness-like delayed-type hypersensitivity reactions like myalgia, arthralgia and/or exanthema occurring between 1 and 14 days after infusion). In case of mild-to-moderate reactions, treatment can be continued with the following measures: the infusion rate should be decreased or temporarily stopped, and pretreatment with oral antihistamines, paracetamol and/or corticosteroids 1 day before and directly before the next infusion should be performed [30, 46, 47].

Up to 8% of patients develop elevated liver enzymes (aspartate/alanine transaminases >150 U/l and more than twice from baseline). With close monitoring, treatment can be continued in most cases (possible if values <3 times the upper limit of normal; with caution if values are 3–5 times the upper limit of normal; stop if values are >5 times the upper limit of normal).

More than 50% of patients develop anti-nuclear antibodies and about 17% anti-dsDNA antibodies. In case of a lupus-like syndrome (45% cutaneous, 55% systemic) where also other autoantibodies occur, treatment should be discontinued as soon as the diagnosis is made, which leads to a resolution in 94% of cases after 3 weeks to 6 months [48, 49].

In severe disease with pulmonary, renal, neurological disease, an additional initiation of corticosteroids and/or immunosuppression might be necessary. Rechallenging with another TNF inhibitor might be a potential option [50–53].

In case of infection during treatment, interrupt IFX temporarily. In case of pregnancy, IFX should normally be stopped until the end of pregnancy. In women of childbearing age, reliable contraception is required until 6 months after the last infusion. IFX should be discontinued 4–8 weeks prior to and may be restarted 2–3 weeks after a live attenuated vaccination. Patients should be informed about the potential risk for serious and atypical infections and in case of symptoms should seek medical advice.

Absolute Contraindications

- Active tuberculosis
- Significant active infection
- Active chronic hepatitis B
- Heart failure (NYHA grade III/IV)
- Hypersensitivity to IFX, murine proteins or any component of the formulation
- Pregnancy or breast-feeding

Relative Contraindications

- Demyelinating diseases
- Live attenuated vaccines
- >200 PUVA treatments (especially if followed by cyclosporine use)
- Malignancies (apart from successfully treated non-melanoma skin cancer and cervical dysplasia) or lymphoproliferative disorders
- Hepatobiliary disorders
- Hepatitis C

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis where UVB and PUVA or one of the systemic therapies (cyclosporine, MTX, acitretin) and a TNF-α blocker (e.g. ETA) showed no therapeutic success. The treatment has to be stopped in case of lacking therapeutic success after 14 weeks. The maximum duration of treatment is 1 year. In case of psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics. Cost coverage has to be granted by the patient's health insurance.

Secukinumab

SEC (Cosentyx®) is a fully human monoclonal IgG1 antibody that binds and antagonizes the cytokine IL-17A. It can be prescribed to patients with moderate-to-severe

Table 13. Overview of important side effects of secukinumab [30]

Frequency	Side effect
Very frequent	Nasopharyngitis
Frequent	Upper respiratory tract infections, rhinitis, pharyngitis, rhinorrhea, oral herpes, diarrhea, urticaria
Occasional	Neutropenia, oral candidosis, tinea pedis, esophageal candidosis, conjunctivitis, elevated transaminases, elevated bilirubin
Rare	None
Very rare	None
Frequency not reported (causal connection unclear)	Exacerbation of Crohn's disease, anaphylaxis, staphylococcal skin infections

psoriasis who failed UVB and PUVA or one of the following systemic therapies: CsA, MTX, acitretin.

The recommended dosage is 300 mg s.c. at week 0, 1, 2 and 3 for induction, followed by 300 mg s.c. every 4 weeks for maintenance of treatment starting in week 4 [54].

In case of infection during treatment, interrupt temporarily, and in case of pregnancy, stop until the end of pregnancy and breast-feeding. Patients should be informed about the potential risk for serious and atypical infections and in case of symptoms should seek medical advice [55].

The removable cap of the Cosentyx SensoReady® pen and the Cosentyx prefilled syringe contain natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals (table 13).

Absolute Contraindications
- Active tuberculosis or acute, severe infections
- Live attenuated vaccines
- Active chronic hepatitis B
- Pregnancy/breast-feeding
- Hypersensitivity to secukinumab

Relative Contraindications
- Crohn's disease (monitor closely)
- Malignancies (apart from successfully treated non-melanoma skin cancer and cervical dysplasia) and lymphoproliferative disorders

With lack of data or recommendations, the following medical states should be considered very carefully: latent tuberculosis, hepatitis C and HIV.

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis who did not experience therapeutic success with UVB and PUVA or one of the following systemic therapies: cyclosporine, MTX, acitretin. The treatment has to be stopped in case of no therapeutic success after 12 weeks. For psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics. Cost coverage has to be granted by the patient's health insurance.

Ustekinumab

UST (Stelara®) is a recombinant, fully human IgG1κ antibody with high specificity and affinity to the p40 subunit of IL-12 and IL-23. It can be prescribed to patients with moderate-to-severe psoriasis who failed a prior treatment with at least one conventional systemic drug or phototherapy. UST is also registered for psoriatic arthritis.

The recommended dosage is 45/90 mg s.c. at weeks 0 and 4 for induction, followed by 45/90 mg s.c. every 12 weeks for maintenance of treatment (i.e. 45 mg in patients <100 kg body weight, 90 mg in patients ≥100 mg body weight). As the price of the 45- and 90-mg doses is the same now in Switzerland, dose adjustment of patients receiving 45 mg with insufficient response to 90 mg every 12 weeks may be beneficial [56].

In case of infection during treatment, stop temporarily, and in case of pregnancy, stop until the end of pregnancy. UST should be discontinued 15 weeks prior to live attenuated vaccination or pregnancy. It may be restarted 2 weeks after live attenuated vaccination. Patients should be informed about the potential risk for serious and atypical infections and in case of symptoms should seek medical advice.

The removable cap of the prefilled syringe contains latex which may cause an allergic reaction in latex-sensitive individuals (table 14).

Absolute Contraindications [4]
- Hypersensitivity to the active substance or to any of the excipients
- Clinically important active infection including untreated latent tuberculosis

Relative Contraindications [4]
- Malignancies (apart from successfully treated non-melanoma skin cancer and cervical dysplasia) and lymphoproliferative disorders
- Pregnancy
- Live vaccines

Table 14. Overview of important side effects of UST [30]

Frequency	Side effect
Very frequent	None
Frequent	Upper respiratory tract infections, nasopharyngitis, erythema and pain at injection site, pruritus, dental infections, dizziness, headache, sore throat, diarrhea, myalgia, arthralgia, fatigue, nausea, vomiting
Occasional	Herpes zoster, viral upper respiratory tract infections, cellulitis, pustular psoriasis, injection site reactions (swelling, pruritus, induration, bleeding, hematoma), depression, facial palsy, allergic reactions including rash and urticaria, rhinitis, exfoliative dermatitis
Rare	Severe allergic reactions including anaphylaxis and angioedema, exfoliative dermatitis (erythroderma)
Very rare	None

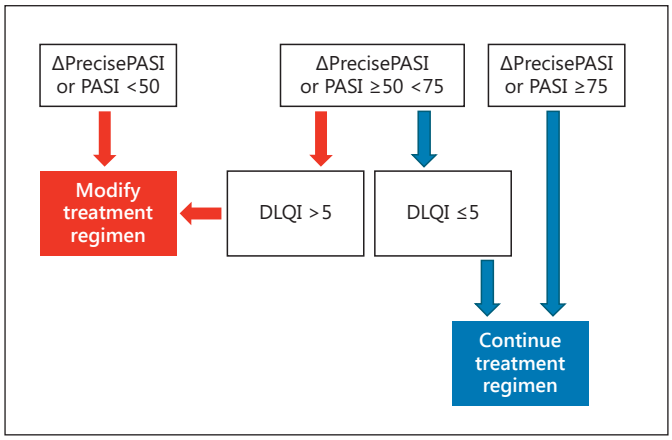


Fig. 1. Current treatment goals, adapted from [59], modified by adding the PrecisePASI.

Limitation (FOPH)

Treatment of adults with severe plaque-type psoriasis who did not experience therapeutic success with UVB and PUVA or one of the following systemic therapies: cyclosporine, MTX, acitretin. The treatment has to be stopped in case of lacking therapeutic success after 3 injections. For psoriasis it can only be prescribed by dermatologists or dermatological university hospitals/outpatient clinics. Cost coverage has to be granted by the patient's health insurance.

Treatment Goals and Transitioning between Systemic Drugs

Goals for Short-Term Efficacy

Before the decision for a systemic therapy of any kind is made, the expectations of both patient and physician should be considered, as this is crucial for the choice of treatment and adherence. This conversation should cover e.g. efficacy, side-effects, preference of oral versus injectable drugs, monitoring, comorbidities and costs. Tables 1 and 2 show the widely variable PASI75 and PASI90 responses after 10–24 weeks [20, 24, 57, 58]. Where head-to-head studies are lacking, direct comparison between drugs is not advisable.

In case where moderately efficacious drugs yield significant additional advantages such as oral intake, few side effects and/or potentially cheap long-term therapy, the achievement of PASI75 or PASI90 within 3 months might play a secondary role. For newer, expensive drugs such as all the biologicals and novel small molecules, a high efficacy should be expected and taken into account when evaluating the treatment response. A recent European consensus [59] goal (modified by adding the PrecisePASI) is useful and is utilized regularly in the tertiary centers in Switzerland. The aim of effective treatment (fig. 1) is a PASI reduction from baseline to time of evaluation (ΔPASI) as well as a reduction of the DLQI. If after an induction phase of up to 16 weeks (depending on medication) these end points are met, the medication can be continued. If the PASI value is not improved by at least 50%, or if the DLQI is still more than 5 points and the PASI response is between 50 and 75%, the treatment regimen is not satisfactory and needs to be modified. If the DLQI is below 5 points, the treatment regimen could be continued even if the PASI response is between 50 and 75% [17]. In the future, those thresholds might even be increased (online suppl. fig. 1) to PASI90 and Precise PASI90 and DLQI <5 as main goals of treatment [24, 57, 60]. As quality of life is an important goal in the treatment, and adherence should also be considered in defining a severe psoriasis in patients not having reached PASI of 10, we recommend that patients fill out the DLQI (Appendix 1) prior to consultation [61–63]. Different language versions of the DLQI (for English, German, French and Italian see the online suppl. material) can be found online: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-different-language-versions/.

Goals for Long-Term Efficacy

For 52 weeks every 3 months and thereafter every 6 months, the same evaluation should be performed and the treatment strategy reevaluated. A potential future goal of reaching PASI90 within 52 weeks after starting therapy seems achievable with newer therapies. However, all options should be considered and discussed with the patient, including keeping alternative drug options available in case a switch should be required later on.

Drug Transitioning

Optimizations of small molecule therapies include the combination of the best effective dose and the lowest rate of possible side effects (see each systemic medication) suggested by the progressive psoriasis initiative as an evidence-based consensus on treatment optimization and transitioning [64].

Transitioning from small molecules (MTX, CsA, acitretin) therapy to biological therapy can in most cases be performed without a washout period or even overlapping if no safety issues arise. APR was not discussed in this work. Combining conventional systemic therapy with biological therapy is currently considered off-label treatment. Nevertheless, this strategy is often used to improve efficacy, optimize the risk-benefit profile, reduce the risk of immunogenicity (with MTX) [41] and improve long-term disease management. Monitoring should be the same as for monotherapy with intervals defined by the agent with more stringent monitoring criteria. If synergistic toxicity is suspected, more frequent monitoring intervals may be required and additional monitoring parameters added. Switching between biologicals due to failure is recommended without a washout period at the time of the next scheduled dose. In case of switching from UST to another biological, the new drug can be used as early as 2–4 weeks after the last dose of UST.

Temporary Treatment Interruptions

Long-term disease control is achieved with a continuous therapy adjusted to the pathogenesis, comfortable drug intake, long-term safety with minimal pharmaceutical interactions and minimal monitoring. Temporary interruption of systemic therapy can be considered with careful follow-up (please note: in CsA therapy, careful dose reduction is indicated due to the risk of rebound of disease). Recurrence can be expected within 2–6 months. Before interrupting or stopping a certain therapy, all relevant factors should be considered, name ly comorbidities including the presence of psoriatic arthritis, individual risk factors, long-term safety, prior course of disease, especially the pattern of flares and rebounds, availability of other treatment options in case of rebound (and/or lower response after treatment reinitiation) and patients' preference. Recurrence of limited disease may be controlled with topical therapy, systemic therapy should be reintroduced if the Physician's Global Assessment appears to be >2 and/or PASI ≥5 and/or DLQI ≥5 or in case of rapid recurrence.

Adjusting Dose and Intervals of Biological Therapy

Dose reduction during successful biological monotherapy can be considered, but there is a risk of loss of efficacy due to immunogenicity by neutralizing antidrug antibody formation [44], especially in case of infliximab and adalimumab. Dosing intervals have been lengthened with ADA and ETA, but this is not recommended for IFX and UST. Dose reduction is possible for IFX down to a minimum of 3 mg/kg body weight, for UST in patients who are treated with 90 mg s.c. every 12 weeks and for ETA in patients who are treated with 50 mg s.c. every week or 25 mg s.c. biweekly. Strategies for nonresponders are to increase the dosage for ADA (40 mg every other week to 40 mg every week), for ETA (50 mg every week to 50 mg biweekly), for UST (45 mg every 12 weeks to 90 mg every 12 weeks [56], with the possibility to further decrease the intervals to every 8 weeks [65]) and for IFX (interval reduction from every 8 weeks to every 6 weeks and in special cases an increase in dose >5 mg/kg body weight). These strategies can increase costs of treatment enormously, therefore secondary loss of response due to immunogenicity has to be ruled out [66]. Combination of small molecules with biologicals is discussed above.

Comorbidity Screening

In recent years comorbidities of psoriasis like psoriatic arthritis, cardiovascular disease and risk factors including obesity, arterial hypertension, dyslipidemia and type 2 diabetes mellitus, nonalcoholic fatty liver disease, inflammatory bowel disease, lymphoma and skin cancer, anxiety and depression, tobacco and alcohol consumption have attracted particular interest.

To prevent progression and treat psoriasis-associated comorbidities as early as possible, an integrated management is required that also takes the side effects of systemic treatments for psoriasis such as arterial hypertension or hyperlipidemia into account. Additionally, medication which can worsen psoriasis like β-blockers, angiotensin-

converting enzyme inhibitors, antimalarials, lithium, interferons, and less commonly contraceptives or nonsteroidal antirheumatic drugs should be ruled out, especially in newly arising forms of psoriasis. Lastly, uncontrolled interruption of systemic corticosteroid treatment should be considered as a risk factor for flares of psoriasis. Six-monthly screening intervals for comorbidities have been suggested in patients with systemic treatment and every 12 months in patients receiving topical treatment (non-interfering with the recommended control intervals during different treatments) [67] (table 15).

Psoriatic arthritis is a common comorbidity in psoriasis patients (up to 41%) and supposed to be underdiagnosed [68]. We recommend the use of a fast and simple screening tool for psoriatic arthritis, e.g. the PEST assessment (Psoriasis Epidemiology Screening Tool) which the patients can fill out prior to consultation (Appendix 2; see also online suppl. material for different language versions) or at least to routinely ask for joint and back pain [69, 70].

Table 15. Laboratory screening for comorbidities

Complete blood count
Liver enzymes: alanine transaminase, aspartate transaminase, γ-glutamyltransferase, alcaline phosphatase
Renal function: creatinine, estimated glomerular filtration rate
Weight, height, and waist circumference
Blood pressure
Hemoglobin A_{1c}, fasting blood glucose
Lipids: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides

End Notes

Guidelines are intended for use by clinicians, dermatologists in private practice and other specialists involved in the treatment of patients with psoriasis vulgaris and also provide a guide for health insurers and policy-makers.

The description of selected therapies (tables 16, 17) is intentionally restricted to the most relevant aspects in the opinion of the guidelines' expert committee. Certain aspects which are not listed separately but might be of interest are assumed to be a part of the physician's duty of care.

Physicians are advised to carefully read the package insert and manufacturer information and to determine whether dosage recommendations and other information contained in the guidelines, such as contraindications and drug interactions, are complete and current. Correct dosage and administration are solely the responsibility of the administering physician.

Science and medical research are under constant development, and our knowledge is constantly growing. In case of any inaccuracies we kindly ask the readers of this guideline to inform us. We took great care to ensure that this guideline represents current knowledge [3].

Acknowledgments

We thank Prof. Philip S. Helliwell, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK, for getting formal permission for using the PEST assessment and Prof. Andrew Finlay, Department of Dermatology, Cardiff University School of Medicine, Cardiff, UK, for getting formal permission for using the DLQI score in our guideline.

The planned translation in the national languages of the guideline will be supported by educational grants of AbbVie, Janssen, and Pfizer to the Department of Dermatology, University of Zurich. The pharmaceutical industry had no influence on the content of the guideline.

Disclosure Statement

Nikhil Yawalkar has served as an investigator, speaker, and/or advisor for AbbVie, Amgen, Celgene, Eli Lilly, Galderma, Janssen, Leo Pharma, MSD, Pfizer, Novartis, and does not hold any shares or other financial interest in any related pharmaceutical company. Mark Anliker served as an investigator, speaker, and/or advisor for AbbVie, Janssen, Merck, Celgene, Novartis, and does not hold any shares or other financial interest in any related pharmaceutical company. Wolf-Henning Boehncke has served as advisor and/or speaker for Abbvie, Almirall, Amgen, Celgene, Janssen, Leo, Lilly, MSD, Novartis, and Pfizer. Luca Borradori has no conflict of interest related to the subject. Curdin Conrad has served as consultant, paid speaker, and/or principal investigator in clinical trials for AbbVie, Actelion, Amgen, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, MSD, Novartis, and Pfizer. Michel Gilliet has no conflict of interest related to the subject. Peter Häusermann has no conflict of interest related to the subject. Peter Itin has no conflict of interest. Emmanuel Laffitte served as an investigator, speaker, and/or advisor for AbbVie, Abbott, Janssen, MSD, Pfizer, Celgene, Novartis, Leo, Amgen, Eli Lilly, and does not hold any shares or other financial interest in any related pharmaceutical company. Carlo Mainetti served as an advisor and/or speaker for AbbVie, Abbott, MSD, Celgene, Novartis, Leo Pharma, Amgen, and Eli Lilly. Lars E. French has served as consulting, advisory, and/or principal investigator for AbbVie, Amgen, Celgene, Actelion, Janssen-Cilag, and Novartis. Alexander Navarini has served as an investigator, speaker, and/or advisor for AbbVie, Janssen, MSD, Pfizer, Celgene, Novartis, Amgen, Actelion, and does not hold any shares or other financial interest in any related pharmaceutical company. Antonios Kolios has served as an investigator, speaker, and/or advisor for AbbVie, Abbott, Janssen, Eli Lilly, MSD, Pfizer, Celgene, Novartis, Actelion, Leo, Amgen, Alk-Abello, and does not hold any shares or other financial interest in any related pharmaceutical company.

Table 16. Small molecules

	Methotrexate	Acitretin	Fumaric acid esters	Cyclosporine A	Apremilast
Mode of action	Folate analog acts as immunosuppressive by inhibiting the dihydrofolate reductase and leading to inhibition of DNA synthesis	Antiproliferative effect on keratinocytes by binding to nuclear RAR and RXR receptor	Anti-inflammatory and cytoprotective via e.g. Nrf2 induction, NF-κB inhibition, action on immune/glial and endothelial cells and keratinocytes	Immunosuppressive via inhibition of calcineurin/ NFAT pathway and JNK signaling, esp. in T cells	Phosphodiesterase-4 inhibition results in cAMP increase in immune and nonimmune cells, leading to decreased expression of inducible NOS, TNF-α, IL-23 and increased IL-10
Registration in dermatology [30]	Severe psoriasis unresponsive to phototherapy or acitretin	Severe pustular and plaque psoriasis	Moderate-to-severe plaque psoriasis unresponsive to topicals [71] (Germany only)	Severe psoriasis unresponsive to other therapies	Moderate-to-severe plaque psoriasis which failed MTX, CsA, acitretin or PUVA
Prior treatment initiation [5, 72]	Full blood count, transaminases, creatinine, urine analysis, β-HCG, CRP, HBs-Ag, HBs-Ab, HBc-Ab, HCV screening, HIV, chest X-ray	Blood count, transaminases, creatinine, fasting blood lipids, fasting glucose, β-HCG (once monthly up to 2–3 years after stop of therapy)	Blood count, transaminases, creatinine, β-HCG, urine analysis	Blood count, transaminases, creatinine, electrolytes incl. Mg, K, urine analysis, lipids, uric acid, HBs-Ag, HBs-Ab, HBc-Ab, HCV screening, HIV, blood pressure at two different time points, β-HCG	Screening for HBs-Ag, HBs-Ab, HBc-Ab, HCV and HIV; creatinine, β-HCG Optional: blood count, transaminases, CRP, IFN-γ release test (tuberculosis)
Laboratory values, control intervals [5]	Differential blood count, creatinine, liver values, CRP after 1, 2, 3, 4, 5, and 12 weeks, then every 3 months; fibroscan every 1.5 g of cumulative dose of MTX [64]	Blood count every 8 weeks, liver values after 4, 8, then every 8 weeks, pregnancy test 1 × monthly, lipids after 4, then every 12 weeks	Blood count, liver/kidney values, urine analysis monthly until month 4, then every 8 weeks	Blood count, transaminases, electrolytes (Mg, K), creatinine, urine at weeks 2, 4, then every 4 weeks; uric acid every 4 weeks, lipids every 4 weeks; blood pressure after 2, 4, 6, 8, 10, and 12 weeks, then every month	Optional: blood count, CRP, AST/ALT, creatinine
Administration	p.o. and s.c.	p.o.	p.o.	p.o.	p.o.
Dosage [5]	Induction with 7.5–15 mg/ week, maintenance up to 25 mg/week as needed; 24–48 h after application 5 mg folic acid orally, in case of ongoing gastrointestinal complaints also 24 h before MTX	Induction with 0.3–0.5 mg/ kg/day for 4 weeks, then 0.5–0.8 mg/kg/day	Induction with 1 tablet Fumaderm® initial (30 mg) daily and increase weekly with 1 tablet until 1–1–1 for 1 week, switch to 1 tablet Fumaderm® (120 mg) daily and increase weekly with 1 tablet up to 2–2–2 (see table 7)	Induction with 2.5–3 mg/kg/ day, in case of inefficiency increase dosage with 0.5–1 mg/kg/day up to a maximum of 5 mg/kg/day; interval therapy (8–16 weeks) with a dosage reduction at the end of induction therapy (e.g. 0.5 mg/ kg body weight every 14 days) or continuous long-term therapy with dosage reduction, e.g. 50 mg every 4 weeks after week 12	Induction over 5 days Day 1: 10–0–0 mg Day 2: 10–0–10 mg Day 3: 10–0–20 mg Day 4: 20–0–20 mg Day 5: 20–0–30 mg Day 6 and ongoing/ maintenance: 30 mg twice daily
Median onset of effect [5]	4–6 weeks	4–8 weeks	6 weeks	4 weeks	10 weeks
PASI75 [5]	Week 16: 35–75% [73–75]	Week 12: 25–41% (monotherapy) [76, 77], 94% (re-PUVA) [78]	Week 16: 50–70% [31]	Weeks 8–16: 50–70%, dose-dependent, 3 mg/kg [79, 80]	Week 16: 32–41% [81]
PASI90	Week 10: 19% Week 22: 39% [82]	Up to 40% [83] (time point unclear)	Week 16: 9% [84]	Week 4: at least 40% [85, 86]	Week 16: 9.8% [81]
Contra-indications [5]	Absolute: severe infections, severe liver disease, renal failure, conception (men and women)/breast-feeding, alcohol abuse, bone marrow dysfunction/ hematological changes, immunodeficiency, acute peptic ulcer, significantly reduced lung function, hypersensitivity to MTX Relative: kidney or liver disorders, ulcerative colitis, history of hepatitis, lack of compliance, active desire to have a child for women of childbearing age and men, gastritis, diabetes mellitus, previous malignancies, congestive heart failure Caution in case of: lung diseases, live vaccination, multiple drug consumption	Absolute: severe renal or hepatic dysfunction, hepatitis, women of childbearing age (see chapter acitretin), excessive alcohol consumption, incompatible comedication, unwillingness to cease blood donation during and until 1 year after treatment, hypersensitivity to acitretin Relative: alcohol abuse, diabetes mellitus, contact lenses, childhood, history of pancreatitis, hyperlipidemia (particularly hypertriglyceridemia) and drug-controlled hyperlipidemia, atherosclerosis Caution in case of: tetracyclines because of the risk of pseudotumor cerebri; relative contraindication for MTX	Severe general disease, chronic gastrointestinal diseases, severe liver and kidney diseases, chronic diseases accompanied by disturbances in leukocyte counts and functions, malignancies, pregnant or lactating women, hypersensitivity to FAEs Caution in case of: concomitant use of MTX, retinoids, CsA, psoralen, nephrotoxic medication	Absolute: kidney dysfunction, uncontrolled arterial hypertension, uncontrolled infection, current or past malignancy (exception nonmelanoma skin cancer), hypersensitivity to CsA; relative: liver dysfunction, pregnancy and lactation, concomitant use of substances that interact with CsA, simultaneous phototherapy or PUVA pretherapy with a cumulative dose >1,000 J/cm^2, concomitant use of other immunosuppressants, retinoids, or long-term pretherapy with MTX, uncontrolled chronic hepatitis B (positive HbsAg)	Absolute: rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption, pregnancy/ breast-feeding, hypersensitivity to apremilast, live vaccines Relative: severe renal impairment (creatinine clearance <30 ml/min estimated by the Cockcroft-Gault equation), dose should be reduced to 30 mg once daily, caution in case of depression, underweight at the start of treatment

Table 16 (continued)

	Methotrexate	Acitretin	Fumaric acid esters	Cyclosporine A	Apremilast
Selected side effects and action [5]	Dose reduction in case of stomatitis, nausea, epigastric pain, depression, diarrhea, hair loss; interrupt therapy in case of gastrointestinal bleeding, infections, elevated liver enzymes; stop therapy in case of pneumonitis; leucovorin in case of overdose	Emollients, artificial tears, no contact lenses in case of hypervitaminosis A, cheilitis, conjunctivitis; stop in case of effluvium; diet and lipid-lowering agents in case of hyperlipidemia	Intake with milk in case of gastrointestinal complaints; dose reduction in case of leukocyte counts below 3,000/μl, lymphocyte counts below 500/μl, increase in serum creatinine over 30% of baseline value, proteinuria, persisting eosinophilia of 25% increase; stop if dose reduction does not lead to normalization of these parameters	Increase fluid intake, reduce dose in case of creatinine increase of ≥30%; dental hygiene or stop in case of gingival hyperplasia; ≥200 mg/day in case of hypomagnesemia; reduce CsA by 25% and 2–3 liters of fluids/day in case of hyperpotassemia; reduce CsA by 25% when transaminases are 2 × above the upper limit	Diarrhea (usually transient, use symtomatic therapy if persisting infection has to be ruled out), nausea, urinary tract infection, bronchitis, upper respiratory tract infections, nasopharyngitis, lack of appetite, insomnia, migraine, headache, cough, vomiting, dyspepsia, frequent defecation, epigastralgia, back pain, fatigue, hypersensitivity, exanthema, weight loss
Cost per year, CHF	Up to 2,100 (15 mg/week excluding folic acid supplements) [30]	1,267 (35 mg/day) [30]	7,196 (6 tablets/day)	3,487 (200 mg/day, 3 mg/kg in a 66-kg person) [30]	13,702.75 (incl. starter pack)
Therapy duration [5]	Not limited	Not limited	Not limited	Upper limit of 12 (max. 24) months in inflammatory diseases (calcineurin inhibitor-induced nephrotoxicity and increased carcinogenesis) [87]	Not limited
Interruption	Yes	Yes	Yes	Yes	Yes
Use in HBV patients [72]	Possible, with gastroenterology	Possible, with gastroenterology	Possible, with gastroenterology	Possible, with gastroenterology	Data insufficient
Use in HCV patients [88]	Not recommended	Second line, with gastroenterology	Data insufficient	Third line, with gastroenterology	Data insufficient
Use in HIV patients [89]	Third line, with infectiology	Second line, with infectiology	Data insufficient	Third line, with infectiology	Data insufficient
Use in latent tuberculosis patients	Possible, with infectiology	Possible, with infectiology	Possible, with infectiology	Possible, with infectiology	Data insufficient
Clinical evaluation	PASI (PrecisePASI for lower BSA ranges), DLQI after 12 and 24 weeks [24, 106, 107]				

p.o. = Per os; s.c. = subcutaneously; h = hour; CHF = Swiss francs; PASI = Psoriasis Area and Severity Index; BSA = body surface area; DLQI = Dermatology Life Quality Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Table 17. Biological therapies

	Anti-TNF-α			Anti-p40 (IL-12/23)	Anti-IL-17A
	Enbrel®	Remicade®	Humira®	Stelara®	Cosentyx®
Generic name	Etanercept ETA	Infliximab IFX	Adalimumab ADA	Ustekinumab UST	Secukinumab SEC
Producer	Pfizer	Centocor/MSD	AbbVie AG	Janssen	Novartis
Mode of action	Human TNF receptor Fc fusion protein which binds soluble/membrane-bound TNF-α and lymphotoxin-β	Chimeric monoclonal IgG1, binds soluble and membrane-bound TNF-α	Human monoclonal IgG1 antibody, binds soluble and membrane-bound TNF-α	Human monoclonal IgG1 antibody, binds and blocks p40 of IL-12 und IL-23 [90]	Fully human monoclonal IgG1 antibody, binds and blocks IL-17A
Registration in dermatology [30]	Plaque-type psoriasis in adults, in case of ETA, IFX, ADA, and UST also psoriatic arthritis, in case of ETA indicated from the age of 6 years				
Swiss health insurance coverage	Yes (IFX: in case of failure of previous TNF inhibitor treatment)				
Limitation for reimbursement [17]	PASI >10 or BSA >10% and/or DLQI >10 and unsatisfactory response to phototherapy or 1 prior systemic treatment (like CsA, MTX, acitretin); in case of IFX also failure to one other TNF blocker in label for psoriasis; see each medication for detailed information				
Galenic form	Prefilled syringe, pen	Lyophilisate	Prefilled syringe, pen	Prefilled syringe	Prefilled syringe, pen
Prior treatment initiation	Full blood count, liver enzymes, creatinine, urine analysis, urine pregnancy test, CRP/ESR; optional: ANA; screening for HBV, HCV, HIV, and tuberculosis, incl. chest X-ray				
Laboratory values [81]	Full blood count, CRP, liver transaminases, creatinine, urine analysis, β-HCG				
Control intervals	Months 1, 3, then every 3 months	Before every infusion	Months 1, 3, then every 3 months	Before each injection	Months 1, 3, then every 3 months
Administration	s.c.	i.v.	s.c.	s.c.	s.c.
Dosage	1 × 50 mg/week or 2 × 25 mg/week [91]; alternative 2 × 50 mg/week for 12 weeks; 0.8 mg/kg/week in children	5 mg/kg in weeks 0, 2, 6, then every 8 weeks; combination with MTX can prolong drug survival [41]	80 mg in week 0, 40 mg in week 1, then every 2 weeks 40 mg	Weeks 0 and 4, followed every 12 weeks: 45 mg s.c. <100 kg, 90 mg s.c. ≥100 kg	300 mg in weeks 0, 1, 2, 3, followed every 4 weeks, starting in week 4

Table 17 (continued)

	Anti-TNF-α			Anti-p40 (IL-12/23)	Anti-IL-17A
	Enbrel®	Remicade®	Humira®	Stelara®	Cosentyx®
Median onset of effect [5]	4–8 weeks	1–4 weeks	4–8 weeks	2–4 weeks [92, 93]	2–3 weeks [54]
PASI75 (few head-to-head studies) [17, 94, 106, 107]	Week 12: 43.5% Week 24: 55.3% (50 mg twice a week)	Week 10: 75–80% [95, 96] Week 24: 69.2%	Week 16: 71–79.6% [75, 97] Week 24: 63.3% [92, 97]	Week 12/24: – 45 mg: 70.1/75.5% – 90 mg: 66.5/75.0%	Week 12: 75–87% Week 16: 86% (300 mg)
PASI90 (few head-to-head studies) [57, 98]	Week 12: 19.3% Week 24: 27.8% (50 mg twice a week)	Week 10: 49.5% Week 24: 50.6%	Week 16: 36.5% Week 24: 45.7%	Week 12/24: – 45 mg: 47.2/58.2% – 90 mg: 35.5/48.5%	Week 12: 59.2% Week 16: 69.8% (300 mg) [54]
Contraindications [17]	Absolute: active tuberculosis, active chronic hepatitis B, significant active infection, pregnancy or breast-feeding (relative in ETA), heart failure (NYHA grade III/IV), hypersensitivity to drug Relative: hepatitis C, malignancies (apart from successfully treated nonmelanoma skin cancer and cervical dysplasia) or lymphoproliferative disorders, live attenuated vaccines, demyelinating diseases, >200 PUVA treatments (especially if followed by cyclosporine use); further: ETA: HIV or AIDS, congestive heart failure (NYHA grade I or II); IFX: hepatobiliary disorders; ADA: history of recurrent infection, underlying conditions predisposing to infections, patients living in geographical areas where tuberculosis and histoplasmosis are widespread, concomitant systemic lupus erythematosus, localized infections, latent tuberculosis			Absolute: hypersensitivity to the active substance or to any of the excipients, clinically important active infection including untreated latent tuberculosis; relative: malignancies (apart from successfully treated nonmelanoma skin cancer and cervical dysplasia) and lymphoproliferative disorders, pregnancy, live vaccines	Absolute: active tuberculosis or acute, severe infections, live vaccines, active chronic hepatitis B, pregnancy/ breast-feeding Relative: Crohn's disease (monitor closely), malignancies (beside basal cell carcinoma), and lymphoproliferative disorders
Antidrug antibodies [99]	1.1–18%, no association with clinical loss of response	19.5–51.5%, association with clinical loss of response	6–46%, association with clinical loss of response	3.8–5.1%, association with clinical loss of response [92, 93]	<1%, no association with clinical loss of response
Potential side effects [30] (selection, not grouped by frequency)	Local reactions to injection site, e.g. in latex allergy, upper respiratory tract infections, pruritus, (thrombo)cytopenia, urticaria, angioedema, lupus, multiple sclerosis, vasculitis, drug rash; in 0.5% paradoxical psoriasis, in 0.1% lupus-like reactions	Up to 20% infusion reactions; viral and bacterial infections including reactivation of opportunistic infections, fever, serum sickness, autoantibodies, lupus-like syndrome, cytopenia, headache, vertigo, exacerbation of demyelinating disorders, flush, gastrointestinal conditions, elevated liver values, spinocellular skin cancer, drug rash, pruritus, paradoxical psoriasis	Local reactions at injection site, rarely angioedema, vertigo, headache, fever, fatigue, bacterial and viral infections, cytopenia, elevation of liver enzymes, lupus-like syndrome, neurological symptoms including paresthesias, multiple sclerosis, paralysis of the face, lymphoma, solid organ tumors, spinocellular skin cancer, malignant melanoma	Local reaction at the injection site, upper respiratory tract infection, cellulitis, depression, vertigo, headache, pharyngolaryngeal pain, diarrhea, pruritus, back pain, myalgia, fatigue [90]	Upper respiratory tract infections, rhinitis, rhinorrhea, oral herpes, diarrhea, urticaria, neutropenia, oral candidiasis, tinea pedis, esophageal candidiasis, conjunctivitis, elevated transaminases, elevated bilirubin, immunogenicity, exacerbation of Crohn's disease, anaphylaxis, staphylococcal skin infections
Use in HBV-infected patients [100, 101]	Yes, during continued use of HBV therapy started 3 months before biological therapy; HBV DNA and liver function tests every 2 months, together with gastroenterology; most evidence for ETA			Case-specific decision	Data insufficient
Use in HCV-infected patients [100, 101]	Yes, monitor liver function and HCV RNA, treat together with gastroenterology; most evidence for ETA			Case-specific decision	Data insufficient
Use in HIV-infected patients	Possible, case-specific decision, together with infectiology [89, 102]			Data insufficient	Data insufficient
Use in latent tuberculosis patients	Requires therapy with isoniazid and vitamin B_6 for 9 months, start of biological possible after 1 month [103, 104]; ETA potentially safer than ADA and IFX [105]				
Interactions	Anakinra, abatacept			None known	Dose of drugs which interact with CYP450 3A4, 1A2 or 2C9 should be evaluated
Costs per year (first year including induction phase) [30], CHF	24,516 (30,174) (50 mg twice a week until week 12, then every week)	19,941 (29,912) (5 mg/kg in 80-kg person)	21,232 (22,866)	17,724 (22,156) (45 mg = 90 mg)	22,314 (26,033)
Interruption	Yes	Not recommended	Possibly	Not recommended	Data insufficient
Risk of cancer	Cancer risk is slightly elevated for nonmelanoma skin cancers and potentially hematological cancers [106], but not other tumors [107]				Data insufficient
Clinical evaluation	PASI (PrecisePASI for lower BSA ranges), DLQI after 12 and 24 weeks [24, 106, 107]				

s.c. = Subcutaneously; i.v. = intravenously; CHF = Swiss francs; PASI = Psoriasis Area and Severity Index; BSA = body surface area; DLQI = Dermatology Life Quality Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TNFα = tumor necrosis factor alpha; ETA = etanercept; ADA = adaliumumab; IFX = infliximab; UST = ustekinumab; SEC = secukinumab; MTX = methotrexate; CsA = cyclosporin A.

Appendix 1: Dermatology Life Quality Index

DLQI

Hospital No.: Date: Score:
Name: Diagnosis:
Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant	☐
	If 'No', over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐

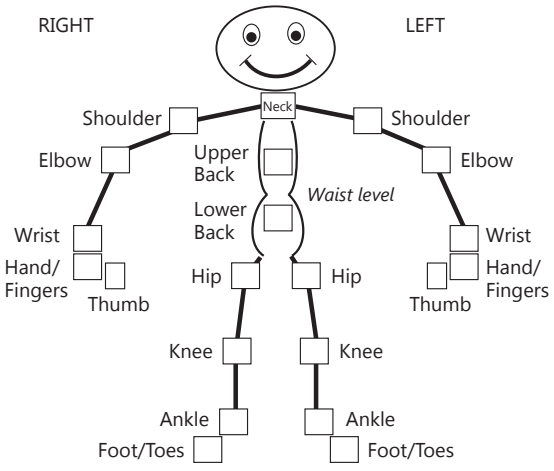
Please check you have answered EVERY question. Thank you.

Appendix 2: PEST Score

Psoriasis Epidemiology Screening Tool (PEST)
Screening questionnaire for psoriasis arthritis in psoriatic patients

	No	Yes
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your fingernails or toenails have holes or pits?		
Have you had pain in your heel?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen, or painful joints):



From Helliwell [70].

References

1 Navarini AA, Kuenzli S, Yawalkar N, Laffitte E, Trüeb RM: Biologics pour le psoriasis: mise au point et recommandations. Dermatologica Helvetica 2009;10:13–16.

2 Navarini AA, Trüeb RM: Therapie der Plaque-Psoriasis. 2. Biologika. Ther Umsch 2010;67:153–165.

3 Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, Sterry W, Streit V, Augustin M, Erdmann R, Klaus J, Koza J, Muller S, Orzechowski HD, Rosumeck S, Schmid-Ott G, Weberschock T, Rzany B: S3-guidelines for the treatment of psoriasis vulgaris update 2011. J Dtsch Dermatol Ges 2011;9(suppl 2):S1–S104.

4 Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, Arenberger P, Bachelez H, Barker J, Dauden E, de Jong EM, Feist E, Jacobs A, Jobling R, Kemeny L, Maccarone M, Mrowietz U, Papp KA, Paul C, Reich K, Rosumeck S, Talme T, Thio HB, van de Kerkhof P, Werner RN, Yawalkar N: European S3-guidelines on the systemic treatment of psoriasis vulgaris – update 2015 – short version – EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015;29:2277–2294.

5 Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, Sterry W, Streit V, Augustin M, Erdmann R, Klaus J, Koza J, Muller S, Orzechowski HD, Rosumeck S, Schmid-Ott G, Weberschock T, Rzany B; Deutsche Dermatologische Gesellschaft, Berufsverband Deutscher Dermatologen: S3 – guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges 2012;10(suppl 2):S1–S95.

6 Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA: Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. N Engl J Med 1974;291:1207–1211.

7 Brockow T, Schiener R, Franke A, Resch KL, Peter RU: A pragmatic randomized controlled trial on the effectiveness of low concentrated saline spa water baths followed by ultraviolet B (UVB) compared to UVB only in moderate to severe psoriasis. J Eur Acad Dermatol Venereol 2007;21:1027–1037.
8 Buckley DA, Healy E, Rogers S: A comparison of twice-weekly MPD-PUVA and three times-weekly skin typing-PUVA regimens for the treatment of psoriasis. Br J Dermatol 1995;133:417–422.
9 Serwin AB, Wasowicz W, Chodynicka B: Selenium supplementation, soluble tumor necrosis factor-alpha receptor type 1, and C-reactive protein during psoriasis therapy with narrowband ultraviolet B. Nutrition 2006;22:860–864.
10 Kolios AG, Rusca F, Reisenbauer K, Cozzio A, French LE, Navarini AA: Topical treatment habits in psoriasis patients receiving adalimumab. Dermatology 2012;224:228–230.
11 Petrozzi JW: Topical steroids and UV radiation in psoriasis. Arch Dermatol 1983;119:207–210.
12 Wong RL, Winslow CM, Cooper KD: The mechanisms of action of cyclosporin A in the treatment of psoriasis. Immunol Today 1993;14:69–74.
13 Diette KM, Momtaz TK, Stern RS, Arndt KA, Parrish JA: Psoralens and UV-A and UV-B twice weekly for the treatment of psoriasis. Arch Dermatol 1984;120:1169–1173.
14 Green L, Sadoff W: A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. J Cutan Med Surg 2002;6:95–102.
15 WHO: Psoriasis report, EB133/5, 133rd session, provisional agenda item 6.2. 2013. http://appswhoint/gb/ebwha/pdf_files/EB133/B133_5-enpdf.
16 WHO: Psoriasis resolution, agenda item 13.5, wha 67.9. 2014. http://appswhoint/gb/ebwha/pdf_files/WHA67/A67_R9-enpdf.
17 Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, Franke J, Antoniou C, Arenberger P, Balieva F, Bylaite M, Correia O, Dauden E, Gisondi P, Iversen L, Kemeny L, Lahfa M, Nijsten T, Rantanen T, Reich A, Rosenbach T, Segaert S, Smith C, Talme T, Volc-Platzer B, Yawalkar N: Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res 2011;303:1–10.
18 Bhushan M, Burden AD, McElhone K, James R, Vanhoutte FP, Griffiths CE: Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2001;145:546–553.
19 Rich P, Scher RK: Nail psoriasis severity index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol 2003;49:206–212.
20 Fredriksson T, Pettersson U: Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978;157:238–244.
21 Finlay AY, Khan GK: Dermatology life quality index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210–216.
22 Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C: The 5-point investigator's global assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat 2015;26:23–31.
23 European Medicines Agency: Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. London, November 18, 2004.
24 Kolios AG, French LE, Navarini AA: Detection of small changes in psoriasis intensity with Precise PASI. Dermatology 2015;230:314–317.
25 Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, Barker J, Bos JD, Burmester GR, Chimenti S, Dubertret L, Eberlein B, Erdmann R, Ferguson J, Girolomoni G, Gisondi P, Giunta A, Griffiths C, Honigsmann H, Hussain M, Jobling R, Karvonen SL, Kemeny L, Kopp I, Leonardi C, Maccarone M, Menter A, Mrowietz U, Naldi L, Nijsten T, Ortonne JP, Orzechowski HD, Rantanen T, Reich K, Reytan N, Richards H, Thio HB, van de Kerkhof P, Rzany B: European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23(suppl 2):1–70.
26 Carretero G, Ribera M, Belinchon I, Carrascosa JM, Puig L, Ferrandiz C, Dehesa L, Vidal D, Peral F, Jorquera E, Gonzalez-Quesada A, Munoz C, Notario J, Vanaclocha F, Moreno JC; Psoriasis Group of the AEDV: Guidelines for the use of acitretin in psoriasis. Actas Dermosifiliogr 2013;104:598–616.
27 Gisondi P, Del Giglio M, Cotena C, Girolomoni G: Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158:1345–1349.
28 Celgene Corporation: Prescribing information for Otezla. Summit, Celgene Corporation, 2014.
29 Maza A, Montaudie H, Sbidian E, Gallini A, Aractingi S, Aubin F, Bachelez H, Cribier B, Joly P, Jullien D, Le Maitre M, Misery L, Richard MA, Ortonne JP, Paul C: Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol 2011;25(suppl 2):19–27.
30 Dokumed: Arzneimittelkompendium der Schweiz. Basel, Dokumed, 2015.
31 Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T: Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis – a retrospective study (future). J Dtsch Dermatol Ges 2009;7:603–611.
32 Thaci D, Weisenseel P, Philipp S, Rosenbach T, Rotterdam S, Augustin M, Neureither M, Reich K: Efficacy and safety of fumaric acid esters in patients with psoriasis on medication for comorbid conditions – a retrospective evaluation (facts). J Dtsch Dermatol Ges 2013;11:429–435.
33 Mrowietz U, Altmeyer P, Bieber T, Rocken M, Schopf RE, Sterry W: Treatment of psoriasis with fumaric acid esters (Fumaderm). J Dtsch Dermatol Ges 2007;5:716–717.
34 Baran W, Batycka-Baran A, Zychowska M, Bieniek A, Szepietowski JC: Folate supplementation reduces the side effects of methotrexate therapy for psoriasis. Expert Opin Drug Saf 2014;13:1015–1021.
35 Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P: Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol 2014;41:1049–1060.
36 Zisman DA, McCune WJ, Tino G, Lynch JP 3rd: Drug-induced pneumonitis: the role of methotrexate. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:243–252.
37 Maybury CM, Samarasekera E, Douiri A, Barker JN, Smith CH: Diagnostic accuracy of noninvasive markers of liver fibrosis in patients with psoriasis taking methotrexate: a systematic review and meta-analysis. Br J Dermatol 2014;170:1237–1247.
38 Lynch M, Higgins E, McCormick PA, Kirby B, Nolan N, Rogers S, Lally A, Vellinga A, Omar H, Collins P: The use of transient elastography and fibrotest for monitoring hepatotoxicity in patients receiving methotrexate for psoriasis. JAMA Dermatol 2014;150:856–862.
39 Maurice PD, Maddox AJ, Green CA, Tatnall F, Schofield JK, Stott DJ: Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. Br J Dermatol 2005;152:451–458.
40 Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, Kalstad S, Mikkelsen K, Kvien TK: The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis 2014;73:132–137.
41 Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H: The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford) 2014;53:213–222.
42 Kaymakcalan Z, Sakorafas P, Bose S, Scesney S, Xiong L, Hanzatian DK, Salfeld J, Sasso EH: Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor. Clin Immunol 2009;131:308–316.

43 Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, Estojak J, Molta CT, Freundlich B: Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ 2010;340: c147.

44 Jullien D, Prinz JC, Nestle FO: Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. J Invest Dermatol 2015; 135:31–38.

45 Garces S, Demengeot J, Benito-Garcia E: The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947–1955.

46 Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S: The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003;98:1315–1324.

47 Boyman O, Comte D, Spertini F: Adverse reactions to biologic agents and their medical management. Nat Rev Rheumatol 2014;10: 612–627.

48 Mocci G, Marzo M, Papa A, Armuzzi A, Guidi L: Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. J Crohns Colitis 2013;7:769–779.

49 Williams VL, Cohen PR: TNF alpha antagonist-induced lupus-like syndrome: report and review of the literature with implications for treatment with alternative TNF alpha antagonists. Int J Dermatol 2011;50:619–625.

50 Subramanian S, Yajnik V, Sands BE, Cullen G, Korzenik JR: Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent. Inflamm Bowel Dis 2011;17:99–104.

51 Yanai H, Shuster D, Calabrese E, Mlynarsky L, Tumuluri S, Cohen RD: The incidence and predictors of lupus-like reaction in patients with IBD treated with anti-TNF therapies. Inflamm Bowel Dis 2013;19:2778–2786.

52 Santiago T, Santiago MG, Rovisco J, Duarte C, Malcata A, da Silva JA: A case of infliximab-induced lupus in a patient with ankylosing spondylitis: is it safe to switch to another anti-TNF-alpha agent? Clin Rheumatol 2013;32: 1819–1822.

53 Moran GW, Lim AW, Bailey JL, Dubeau MF, Leung Y, Devlin SM, Novak K, Kaplan GG, Iacucci M, Seow C, Martin L, Panaccione R, Ghosh S: Dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:1002–1024.

54 Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C: Secukinumab in plaque psoriasis – results of two phase 3 trials. N Engl J Med 2014;371: 326–338.

55 Novartis: FDA secukinumab (AIN457) advisory committee briefing material. 2014.

56 Reich K, Puig L, Paul C, Kragballe K, Luger T, Lambert J, Chimenti S, Girolomoni G, Nicolas JF, Rizova E, Brunori M, Mistry S, Bergmans P, Barker J: One-year safety and efficacy of ustekinumab and results of dose adjustment after switching from inadequate methotrexate treatment: the transit randomized trial in moderate-to-severe plaque psoriasis. Br J Dermatol 2014;170:435–444.

57 Puig L: Pasi90 response: the new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol 2015;29:645–648.

58 Van de Kerkhof PC: On the limitations of the psoriasis area and severity index (PASI). Br J Dermatol 1992;126:205.

59 Mrowietz U: Implementing treatment goals for successful long-term management of psoriasis. J Eur Acad Dermatol Venereol 2012; 26(suppl 2):12–20.

60 Torres T, Puig L: Treatment goals for psoriasis: should PASI 90 become the standard of care? Actas Dermosifiliogr 2015;106:155–157.

61 Martinez-Garcia E, Arias-Santiago S, Valenzuela-Salas I, Garrido-Colmenero C, Garcia-Mellado V, Buendia-Eisman A: Quality of life in persons living with psoriasis patients. J Am Acad Dermatol 2014;71:302–307.

62 Hagg D, Sundstrom A, Eriksson M, Schmitt-Egenolf M: Decision for biological treatment in real life is more strongly associated with the psoriasis area and severity index (PASI) than with the dermatology life quality index (DLQI). J Eur Acad Dermatol Venereol 2015; 29:452–456.

63 Takahashi H, Iinuma S, Tsuji H, Honma M, Iizuka H: Biologics are more potent than other treatment modalities for improvement of quality of life in psoriasis patients. J Dermatol 2014;41:686–689.

64 Mrowietz U, de Jong EM, Kragballe K, Langley R, Nast A, Puig L, Reich K, Schmitt J, Warren RB: A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2014;28:438–453.

65 Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wasfi Y, Chan D, Hsu MC, You Y, Poulin Y, Korman N, Prinz JC, Reich K: Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol 2015;172:1371–1383.

66 Carrascosa JM, van Doorn MB, Lahfa M, Nestle FO, Jullien D, Prinz JC: Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. J Eur Acad Dermatol Venereol 2014;28:1424–1430.

67 Dauden E, Castaneda S, Suarez C, Garcia-Campayo J, Blasco AJ, Aguilar MD, Ferrandiz C, Puig L, Sanchez-Carazo JL: Clinical practice guideline for an integrated approach to comorbidity in patients with psoriasis. J Eur Acad Dermatol Venereol 2013;27:1387–1404.

68 Villani AP, Rouzaud M, Sevrain M, Barnetche T, Paul C, Richard MA, Beylot-Barry M, Misery L, Joly P, Le Maitre M, Aractingi S, Aubin F, Cantagrel A, Ortonne JP, Jullien D: Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. J Am Acad Dermatol 2015; 73:242–248.

69 Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS: Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin Exp Rheumatol 2009;27:469–474.

70 Helliwell PS: Psoriasis Epidemiology Screening Tool (PEST): a report from the GRAPPA 2009 annual meeting. J Rheumatol 2011;38: 551–552.

71 Biogen: Fachinformation Fumaderm® initial/fumaderm®. Ismaning, Biogen, 2009.

72 Motaparthi K, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S; Medical Board of the National Psoriasis Foundation: From the medical board of the National Psoriasis Foundation: recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. J Am Acad Dermatol 2014;70:178–186.

73 Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA: Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003; 349:658–665.

74 Nyfors A: Benefits and adverse drug experiences during long-term methotrexate treatment of 248 psoriatics. Dan Med Bull 1978;25: 208–211.

75 Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A: Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558–566.

76 Van de Kerkhof PC, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, Damstra RJ, Combemale P, Neumann MH, Chalmers RJ, Olsen L, Revuz J: The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol 1998;138:84–89.

77 Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ: Side-effect profile of acitretin therapy in psoriasis. J Am Acad Dermatol 1989;20:1088–1093.

78 Saurat JH, Geiger JM, Amblard P, Beani JC, Boulanger A, Claudy A, Frenk E, Guilhou JJ, Grosshans E, Merot Y, et al: Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica 1988;177:218–224.
79 Koo J: A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporin, Neoral and Sandimmun, in patients with severe psoriasis. Olp302 study group. Br J Dermatol 1998;139:88–95.
80 Laburte C, Grossman R, Abi-Rached J, Abeywickrama KH, Dubertret L: Efficacy and safety of oral cyclosporin a (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. Br J Dermatol 1994;130:366–375.
81 Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, Hu C, Day RM: Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Lancet 2012;380:738–746.
82 Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, Reich K: Efficacy and safety of infliximab vs methotrexate in patients with moderate-to-severe plaque psoriasis: Results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011;165:1109–1117.
83 Dubertret L: Retinoids, methotrexate and cyclosporine. Curr Probl Dermatol 2009;38:79–94.
84 Fallah Arani S, Neumann H, Hop WCJ, Thio HB: Fumarates vs methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol 2011;164:855–861.
85 Van Joost T, Bos JD, Heule F, Meinardi MM: Low-dose cyclosporin A in severe psoriasis. A double-blind study. Br J Dermatol 1988;118:183–190.
86 Shintani Y, Kaneko N, Furuhashi T, Saito C, Morita A: Safety and efficacy of a fixed-dose cyclosporin microemulsion (100 mg) for the treatment of psoriasis. J Dermatol 2011;38:966–972.
87 Wu X, Nguyen BC, Dziunycz P, Chang S, Brooks Y, Lefort K, Hofbauer GF, Dotto GP: Opposing roles for calcineurin and ATF3 in squamous skin cancer. Nature 2010;465:368–372.
88 Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF Jr, Gottlieb AB, National Psoriasis Foundation: Treatment of psoriasis in patients with hepatitis C: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol 2009;61:1044–1055.
89 Menon K, Van Voorhees AS, Bebo BF Jr, Gladman DD, Hsu S, Kalb RE, Lebwohl MG, Strober BE: Psoriasis in patients with HIV infection: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol 2010;62:291–299.
90 Centocor: Stelara product information 16.1.2009. http://www.Emea.Europa.Eu/humandocs/humans/epar/stelara/stelara.htm.
91 Van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, Leigheb G, Camacho FM, Forsea D, Zang C, Boussuge MP, Paolozzi L, Wajdula J: Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol 2008;159:1177–1185.
92 Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665–1674.
93 Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675–1684.
94 Griffiths CEM, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118–128.
95 Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB: A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56:31, e1–e15.
96 Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE: Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005;366:1367–1374.
97 Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, Strober BE, Kaul M, Gu Y, Okun M, Papp K: Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008;58:106–115.
98 Puig L, Lopez A, Vilarrasa E, Garcia I: Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. J Eur Acad Dermatol Venereol 2014;28:1633–1653.
99 Carrascosa J-M, van Doorn MBA, Lahfa M, Nestle FO, Jullien D, Prinz JC: Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. J Eur Acad Dermatol Venereol 2014;28:1424–1430.
100 Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF: The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. Br J Dermatol 2013;169:1295–1303.
101 Navarro R, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, Taberner R, Ferran M, Garcia-Bustinduy M, Romero-Mate A, Pedragosa R, Garcia-Diez A, Dauden E: Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. Br J Dermatol 2013;168:609–616.
102 Rustin MH: Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. Br J Dermatol 2012;167(suppl 3):3–11.
103 Beglinger C, Dudler J, Mottet C, Nicod L, Seibold F, Villiger PM, Zellweger JP: Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. Swiss Med Wkly 2007;137:620–622.
104 Tsai TF, Ho V, Song M, Szapary P, Kato T, Wasfi Y, Li S, Shen YK, Leonardi C: The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. Br J Dermatol 2012;167:1145–1152.
105 Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X: Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French research axed on tolerance of biotherapies registry. Arthritis Rheum 2009;60:1884–1894.
106 Patel RV, Clark LN, Lebwohl M, Weinberg JM: Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 2009;60:1001–1017.
107 Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ, Cook EF, Carney G, Schneeweiss S: Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:2757–2764.